ClinicalEvidence

Child health

Measles, mumps, and rubella: prevention

Search date July 2007

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ABSTRACT

INTRODUCTION: Measles virus causes an estimated 21 million infections and 345,000 deaths a year worldwide, with increased risks of neurological, respiratory, and bleeding complications in survivors. Mumps can cause neurological problems and hearing loss, orchitis with infertility, and pancreatitis. Rubella infection is usually mild, but can lead to fetal death or severe congenital abnormalities if contracted in early pregnancy. The incidence of all three infections has decreased significantly in countries with routine immunisation programmes targeted at these diseases, but decreased immunisation rates are associated with increased risks of infection. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of measles immunisation? What are the effects of mumps immunisation? What are the effects of rubella immunisation? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 102 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: MMR immunisation; monovalent measles immunisation; monovalent mumps immunisation; and monovalent rubella immunisation.

QUESTIONS

INTERVENTIONS

Key points

- Measles, mumps, and rubella are viral infections that can all be associated with serious disease in non-immune people.

  Measles virus causes an estimated 21 million infections and 345,000 deaths a year worldwide, with increased risks of neurological, respiratory, and bleeding complications in survivors.

  Mumps can cause neurological problems and hearing loss, orchitis with infertility, and pancreatitis.

  Rubella infection is usually mild, but can lead to fetal death or severe congenital abnormalities if contracted in early pregnancy.

  The incidence of all three infections has decreased significantly in countries with routine immunisation programmes targeted at these diseases, but decreased immunisation rates are associated with increased risks of infection.

- The MMR immunisation is considered to be effective in preventing measles, mumps, and rubella infection, but placebo-controlled studies have not been done and would now be considered unethical.

  The MMR immunisation can cause fever, febrile seizures, and anaphylaxis, with aseptic meningitis more likely after some strains compared with others.

  There is no evidence of an association between the MMR immunisation and risks of asthma, Guillain–Barré syndrome, autism, diabetes, gait disturbance, demyelinating disorders, or inflammatory bowel disease.

- Measles immunisation with monovalent or MMR immunisation is associated with reduced risks of measles, measles-related mortality, and subacute sclerosing panencephalitis.

Seroconversion rates are similar for MMR and monovalent immunisations against measles, mumps, and rubella, but use of monovalent immunisations requires more injections and so may take longer to achieve full protection.

Both the MMR immunisation and naturally acquired measles infection may increase the risk of idiopathic thrombocytopenic purpura.

- The use of MMR, rather than monovalent measles, mumps, and rubella immunisations, provides earlier protection against all three diseases, requires fewer injections over a shorter period of time, and decreases the pool of individuals susceptible to these infections in the community.

DEFINITION

Measles, mumps, and rubella are infectious diseases. **Measles** is caused by a ribonucleic acid paramyxovirus. The illness is characterised by an incubation period of 6 to 19 days (median 13 days), [1] a prodromal period of 2 to 4 days with upper respiratory tract symptoms, conjunctivitis, Koplik's spots on mucosal membranes, and high fever, followed by a widespread maculopapular rash that persists, with fever, for 5 to 6 days. **Mumps** is caused by a ribonucleic acid virus classified as a rubulavirus in the *Paramyxoviridae* family. [1] The illness is characterised by an incubation period of 15 to 24 days (median 19 days), with a prodromal period of non-specific flu-like symptoms preceding the development of parotitis. This swelling, which is frequently bilateral and accompanied by abdominal pain and headache, usually resolves within 7 to 10 days. About one third of mumps infections are subclinical or mild non-specific illnesses not recognised as mumps. [2] **Rubella** is caused by rubivirus, a ribonucleic acid enveloped togavirus in the *Togaviridae* family. There are no animal reservoirs and only one serotype. [1] The incubation period is 15 to 20 days (median 17 days). Although virus is shed from 7 days before to 6 days after the appearance of the rash, the period of infectivity with rubella is not known. The infection is frequently subclinical. [1] In clinical infection, there are often no prodromal symptoms. A generalised lymphadenopathy is followed by a rash up to 7 days later. Babies with congenital rubella syndrome (CRS) may excrete virus for years and therefore be a source of infection. This review focuses on the use of monovalent or MMR immunisation in healthy children from 12 months onwards; use of monovalent or MMR immunisation in immunocompromised children is excluded.

INCIDENCE/ PREVALENCE

The incidence of measles, mumps, and rubella varies according to immunisation coverage. **Measles:** Worldwide, there are an estimated 21 million cases of measles each year, [3] but the incidence is only 0 to 10/100,000 people in countries with widespread immunisation programmes such as the USA, UK, Mexico, India, China, Brazil, and Australia. [4] In the USA, before licensing of effective immunisations, more than 90% of people were infected by the age of 15 years. After licensing in 1963, incidence fell by about 98%. [5] The mean annual incidence in Finland was 366/100,000 in 1970, [6] but steadily decreased since the launch of vaccination in 1982, with three cases in 1995 and no cases in 1996. [7] Similarly, the annual incidence declined to zero in Chile, the English-speaking Caribbean, and Cuba during the 1990s, when immunisation programmes were introduced. [8] [9] **Mumps** predominantly affects children, with 32% of reported cases worldwide in children aged 0 to 4 years and 53% in children aged 5 to 14 years. [10] In the preimmunisation era, by 10 years of age, 87% of the population in England had serological evidence of mumps infection. [11] Since the introduction of the MMR, there has been a decrease in the incidence of disease, such that in some countries (e.g., Finland) there is no longer any indigenous disease. [6] Those cases that still occur are usually in an older age group, who are not immunised. For example, over 56,000 cases of mumps were reported in England and Wales in 2005 (compared with 16,000 cases in 2004). [12] In contrast to figures from 1989 (where 12% of cases occurred in people aged 15 years or over), over 80% of cases in 2005 occurred in this age group. **Rubella:** In the preimmunisation era in the UK, rubella was rare under the age of 5 years, with the peak incidence being between 5 and 10 years of age. [13] Serological surveys around the world found that by late adolescence/early adulthood, 80% of women had been infected. [14]

AETIOLOGY/ RISK FACTORS

Measles is highly contagious, with mumps and rubella being less so. As with most other infectious diseases, risk factors include overcrowding and low herd immunity. **Measles** spreads through airborne droplets. [1] Newborn babies have a lower risk of measles compared with older infants, owing to protective maternal antibodies, although in recent US outbreaks, maternal antibody protection was lower than expected. [5] Antibody levels are lower in babies born to immunised mothers compared with offspring of naturally infected mothers. [15] [16] **Mumps** spreads through respiratory droplets, saliva, and possibly urine. [1] The period of infectivity extends from a few days before the salivary glands become enlarged to about 5 days after. As with measles, the risk of mumps is lower in the first 9 to 12 months of age, owing to the presence of maternal antibodies, although this pattern may change in a largely immunised maternal population. **Rubella** spreads through direct contact or airborne droplets. [1]

PROGNOSIS

Measles: The WHO estimated that measles caused 345,000 deaths and 12.1 million disability-adjusted life years in 2005. [3] **Measles in healthy people:** In resource-rich countries, most prognostic data come from the preimmunisation era and from subsequent outbreaks in non-immunised populations. The overall rate of complications in the UK was 6.7% before the introduction of measles immunisation. Encephalitis affected 1.2/1000 diseased people, and respiratory complications arose in 38/1000 diseased people. [17] Other complications before the introduction of the immunisation included seizures, with or without fever, affecting 5/1000 people with measles. [18] Idiopathic thrombocytopenic purpura (ITP) has been reported, but the frequency is not known. Subacute sclerosing panencephalitis is an inevitably fatal, progressive degenerative disorder of the central nervous system, with a mean onset 7 to 10 years after measles infection. It is more common when measles occurs under the age of 1 year (18/100,000 in children <1 year of age *v* 4/100,000 overall), as identified by a passive reporting system set up in England and Wales to monitor the incidence of subacute sclerosing panencephalitis. [19] Between 1989 and 1991 in the USA, measles resurgence among young children (aged <5 years) who had not been immunised led to 55,622 cases, with more than 11,000 hospital admissions and 166 deaths. [20] [21] [22] Measles complications also include diarrhoea (9%) and pneumonia (6%). [22] Measles during pregnancy results in a higher risk of premature labour, [23] but no confirmed increase in congenital anomalies. [24] **Measles in malnourished or immunocompromised people:** In malnourished people, particularly those with vitamin A deficiency, measles case fatality can be as high as 25%. Immunocompromised people have a higher morbidity and mortality. Children younger than 5 years, and adults older than 20 years, have a higher risk of severe complications and death. [20] [25] In the period between 1974 and 1984, four major paediatric treatment centres in the UK reported that 15/51 (29%) deaths in children in their first remission from leukaemia resulted from measles. [26] Another report reviewing cases from the same four UK centres between 1973 and 1986 found that 5/17 (29%) cases of measles in children with malignancies proved fatal. [27] At least 5/36 (14%) measles-associated deaths in 1991 in the USA were in HIV-infected people. [20] Worldwide, measles is a major cause of blindness, and causes 5% of deaths in young children (aged <5 years). [28] **Mumps:** Deaths following mumps are rare, with about five registered annually in the preimmunisation era in England and Wales (although only half of these were judged to be directly because of mumps). [10] Deaths occurred mainly in people aged over 40 years. The most important complications of mumps are those relating to the central nervous system, the gonads, and the pancreas. Before the introduction of the MMR immunisation in the UK, mumps was one of the most common causes of aseptic meningitis, accounting for about 20% of cases. [29] The outcome was usually benign. Mumps encephalitis is less common and the outcome more serious. [30] A case series (41 children) in Finland found that 2/40 (5%) children had continuing ataxia and 7/42 (17%) had behavioural disturbances at 4 months to 2 years after mumps encephalitis. [31] Sensorineural hearing loss, usually unilateral, occurs after mumps infection, but its prevalence is unknown, although paediatricians in Israel who had observed cases of hearing loss following a mumps epidemic in 1984 suggested that it may be as common as 1/3400 (0.03%). [32] A large population-based study of mumps undertaken in the USA (1310 cases from 1935 to 1974) found orchitis in 10% of males overall, being much more common in adults. [33] Orchitis was bilateral in 17% of men. The study found testicular atrophy in 47/132 (36%) men, of whom two developed testicular neoplasms. A smaller population-based study of mumps in a virgin population (561 Yupik people on St Lawrence Island) found that 52/205 (25%) of men with mumps had orchitis, of which 26 cases were unilateral, 19 bilateral, and seven unknown. [34] Most cases (73%) occurred in males aged 15 years or over, of whom 37% had bilateral disease. In females who had mumps, 15% had mastitis, one third of whom were aged 15 years or over. [34] In a community-based study in the USA (342 cases), the most frequent complication of mumps was pancreatitis, occurring in 12/342 (4%) people, [2] whereas in a case series, 50/109 (46%) people admitted to hospital had clinical signs of pancreatitis. [35] There is an increase in the rate of spontaneous abortion following mumps infection in the first trimester, [24] but no increase in congenital anomalies or prematurity. [23] **Rubella:** Complications of rubella are rare in children. In an epidemic in Japan in 1987, 8250 children under 15 years of age were estimated to have suffered rubella infection. [36] Five children developed encephalitis (one with adverse sequelae), three had meningitis, four had ITP, four had vascular purpura, two had haemolytic anaemia, and eight had pneumonia. Retrospective observational data suggest that ITP may occur at a rate of about 1/3000. [37] Rubella encephalopathy occurs, but rarely, and a case series suggested that long-term sequelae were less frequent than after measles encephalopathy. [38] In children, arthralgia is infrequent; however, in adults, especially women, it is common. A review of hospital records (74 adults with rubella) in London, UK, found that most had arthralgia and 11/74 (15%) had arthritis. [13] Arthritis may be recurrent, but is usually self-limiting. The most serious consequence of rubella infection is congenital rubella syndrome (CRS), first described by Gregg in 1941. [39] Almost any system can be affected by CRS, depending on the stage of pregnancy at which the infection occurs. In a prospective cohort study of over 1000 pregnant women in England and Wales with confirmed rubella infection, the frequency of congenital infection after maternal rubella with a rash during the first 12 weeks of pregnancy was more than 80%, declining to 25% when the infection occurred at the end of the second trimester. [40] Rubella-related defects occurred in all infants infected before the 11th week of pregnancy, in 35% of those infected at 13 to 16 weeks, and in no infants infected later in pregnancy. [40] The earlier in pregnancy the infection occurs, the more serious the defects;

for example, infants infected before the 11th week had both CHD and deafness, whereas infants with later infections only had deafness.

AIMS OF INTERVENTION To eliminate measles, mumps, and rubella infection and CRS, with minimal adverse effects.

OUTCOMES Treatment effectiveness (clinical cases; rates of seroconversion): rates of clinically apparent measles, mumps, and rubella. If no clinical outcomes were available, we reported rates of seroconversion because it is used frequently as a correlate of immunisation efficacy; mortality; complications of infection: related complications including CRS; adverse effects.

METHODS *Clinical Evidence* search and appraisal July 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, Issue 2, 2007. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews, RCTs, and observational studies in the English language. RCTs could be "open" or "blinded", and had to contain 20 individuals or more, of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. For additional information on immunisation strains and branding, see table 1, p 24 . Where possible, original articles were sought and critiqued in preference to non-systematic reviews. Comprehensive or systematic reviews were included. We only included studies involving immunisation strains that are currently widely used. In the benefits section comparing different immunisations and schemes, we included RCTs and stronger observational studies, because after the high clinical efficacy against measles, mumps, and rubella shown in early RCTs, further RCTs have been considered unethical (see benefits of measles immunisation, p 4). We assessed the use of monovalent or MMR immunisation in healthy children from 12 months of age onwards: studies assessing the use of monovalent or MMR immunisation in immunocompromised children were excluded. We included a selection of recent population outbreak studies to show the ongoing effect of measles, mumps, and rubella in terms of disease-related complications, as well as immunisation efficacy; the studies included represent only a small proportion of reports available. In the harms sections, we looked at the MMR immunisation only, and included RCTs and robust observational studies (see harms of measles immunisation, p 4). We have not assessed congenital rubella syndrome as a possible adverse effect of monovalent rubella or MMR immunisation; we will add information on this in future updates of this review. We have not included case reports or articles published in languages other than English. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). This review was undertaken in response to concerns about the possible association of immunisation with specific adverse effects, and the review was structured a priori to look for the evidence on a range of pre-selected adverse effects, as well as any evidence of benefit of immunisation. Therefore, this review differs in perspective from other *Clinical Evidence* systematic reviews, which weigh the evidence of benefits and harms on an equal footing without such prior selection. In view of the different perspective that this review takes (i.e., focusing on evidence relating to possible harms), we have not GRADED this review, as it would not represent the overall balance of evidence of benefits and harms relating to these interventions. Rather, we have summarised the reported evidence under outcome-based headings, in which the overall balance of the evidence can be more correctly represented.

QUESTION **What are the effects of measles immunisation?**

OPTION **MONOVALENT MEASLES IMMUNISATION OR COMBINED MMR IMMUNISATION**

Treatment effectiveness (clinical cases; rates of seroconversion)
Compared with placebo or no immunisation One quasi-randomised RCT, a nationwide retrospective cohort study, and several population-based studies based in countries with different healthcare systems, and socioeconomic and demographic distributions found consistent evidence that measles immunisation (MMR or monovalent) reduced the incidence of measles infection.

Mortality

Compared with placebo or no immunisation One large cohort study found that measles immunisation is associated with a reduction in mortality compared with no immunisation.

Complications of infection
Compared with placebo or no immunisation One case control study found that a history of measles immunisation was less likely among people with subacute sclerosing panencephalitis (SSPE) than among healthy controls.

Adverse effects
Compared with placebo or no immunisation One RCT, cohort studies, and population-based studies have found that MMR immunisation was associated with increased rates of fever and febrile seizures, although febrile seizures were rare, and there was no evidence of increased rates of afebrile seizures. Observational studies found that MMR containing some immunisation virus strains was associated with an increased risk of aseptic meningitis, and MMR immunisation was also associated with an increased risk of idiopathic thrombocytopenic purpura (ITP) and arthralgia. We found no evidence of an association between MMR immunisation and the risks of developing asthma, type 1 diabetes, Guillain–Barré syndrome, gait disturbance, multiple sclerosis, optic neuritis, autism or autistic spectrum disorders, leukaemia, or inflammatory bowel disease. Anaphylaxis has been reported after immunisation with MMR, but this is rare.

Note:
RCTs using a control group receiving no immunisation or placebo are now deemed unethical because of the existing evidence of efficacy of the MMR immunisation, and because of the potential harms associated with naturally acquired measles, mumps, or rubella infection. Measles causes an estimated 345,000 deaths worldwide annually, with increased risks of neurological, respiratory, and bleeding complications.

Benefits: We found no systematic review. We found one quasi-RCT from the UK comparing monovalent measles immunisation versus no immunisation. [41] We also found one large retrospective cohort study [42] and several other large observational studies [6] [43] [44] assessing measles infection rates in immunised compared with non-immunised children. All found that measles immunisation reduced measles infection rates.

RCTs of measles incidence after MMR or monovalent immunisation:
We found no RCTs comparing the clinical effects of MMR versus no immunisation or placebo. The quasi-RCT conducted in the UK followed 36,211 children aged 10 months to 2 years, for 9 months. [41] Children were allocated according to birth date to live immunisation alone (9538 children); killed immunisation (EEB strain) followed by live immunisation (Schwarz strain; 10,434 children); or no immunisation (16,239 children). The trial found an 85% efficacy over 6-month follow-up in children who had been immunised with either live immunisation alone or killed immunisation plus live immunisation, compared with non-immunised controls (20 cases/1000 immunised children *v* 134 cases/1000 non-immunised children). Follow-up of a subset of these children (live immunisation group [7889 children]; killed plus live immunisation [8171 children]; and non-immunised [5593 children]) found an increase in protective effect 2 years and 9 months after immunisation (94% with live immunisation *v* 88% with killed plus live immunisation) after exposure to two major epidemics. [41] After 15-years follow-up (at 12–27 years after recruitment) of 9106 children, there was a higher incidence of measles in the non-immunised group. [45] The difference between immunised and non-immunised children remained after controlling for subsequent immunisation in initial placebo groups, but it did not remain after controlling for growing herd immunity after mass immunisation (AR: 0.3/1000 person-years with immunisation *v* 1/1000 person-years with no immunisation; P <0.001). The overall protective efficacy was high (92%, 95% CI 86% to 95%) between 1976 and 1990. [45]

Cohort studies of measles incidence after MMR or monovalent immunisation:
One large retrospective cohort study of the entire US population from 1985 to 1992 compared measles infection rates in children who were immunised versus rates in children whose parents had declined immunisation (17,390 cases from an immunised population of 51,264,140 to 52,377,192 from 1985–1992 *v* 2827 cases from a non-immunised population of 234,040 to 245,887 from 1985–1992). [42] The cohort study did not state what proportion of immunised children received monovalent or MMR immunisation, although MMR was already widely used in the USA by 1985. The study found that, although overall measles incidence was low because of herd immunity, immunisation significantly reduced measles infection compared with no immunisation (incidence of measles in immunised group: 0.56–17.59/100,000; incidence in non-immunised group: 5.15–378.33/100,000; RR of measles in non-immunised *v* immunised groups 4–170; all depending on age group and year of survey).

Population-based studies of measles incidence after MMR or monovalent immunisation:
We also found many population-based studies from different countries with different healthcare systems, and different socioeconomic and demographic distributions. [6] [44] [46] [47] [48] [49] [50] These studies consistently found that measles immunisation was associated with a steep decline

in measles infection. In most resource-rich countries, 95% of the population must be immunised to eliminate measles infection. In countries with greater population density, immunisation coverage may need to reach 99% to eliminate measles infection. [51] One time series from the WHO found a global decline in reported measles incidence (which underestimates true incidence) from about 4.5 million per year in 1980 to about 1.0 million per year in 2000. [43] The decline was associated with the rise in reported measles immunisation coverage from about 10% in 1980 to about 80% in 2000. One population-based time series of measles incidence from Finland found that, in a population of about 5 million people, after the introduction of a live monovalent immunisation programme (1975–1981), the number of new measles cases each year fell from an average of 2074 cases between 1977 and 1981, to 44 cases in 1985. [6] This trend continued, with only 13 new measles cases in 1993.Shortly after introducing the MMR programme in Finland in 1982, mumps incidence also fell, from an average of 9366 cases of mumps per year in 1977 to 1981 to fewer than 20 cases per year in 1990 to 1993. Cases of rubella fell from 423 laboratory-confirmed cases in 1984 to 1986, to 25 cases in 1993. [6] One cross-sectional study in Sao Paulo, Brazil, which was repeated before and after a measles immunisation campaign in 1987 (8163 people, strain not reported), found that reported measles incidence fell from 222 per 100,000 in 1987 to 2.7 per 100,000 in 1988. [44] However, measles outbreaks in countries with high immunisation coverage can still occur. Between 1999 and 2000 in the Netherlands, a measles outbreak took place in a school in which only 7% of the children were immunised. [52] Eventually, 94% of non-immunised people from closed communities were affected, amounting to 3292 cases. The Netherlands had one of the lowest rates of measles disease with high immunisation coverage (96%), and the epidemic was attributed to the presence of small non-immunised pockets.

Population-based studies of measles mortality after MMR or monovalent measles immunisation:
We found one cohort study. [53] There are numerous population-based studies evaluating the effects of MMR immunisation on mortality, and we report two representative studies below. [54] [55] The cohort study compared a group of children in Bangladesh immunised with live Schwarz strain monovalent measles immunisation versus age-matched, non-immunised children (8135 matched pairs). [53] It found a significant reduction in mortality with immunisation (16,270 children aged 9–60 months at immunisation; RR for mortality at 43 months 0.54, 95% CI 0.45 to 0.65). A measles outbreak of 1571 cases was reported in 2002 in Campania, Italy, where MMR immunisation coverage was under 70%. [54] The outbreak led to 594 admissions to hospital and four deaths. From December 1999 to June 2000, an outbreak of measles in Dublin, Ireland, led to 1115 notifications and 111 measles-related paediatric hospital admissions. [55] Only one third of the children over the age of 15 months (the age recommended for MMR immunisation) were immunised, and all three deaths reported occurred in non-immunised children.

Case control studies of incidence of subacute sclerosing panencephalitis after MMR or monovalent immunisation:
Rates of subacute sclerosing panencephalitis (SSPE) have fallen considerably wherever they have been monitored after the introduction of measles-containing immunisations. [56] [57] [58] [59] One case control study found that a history of measles immunisation was significantly less likely among people with SSPE than among healthy controls (OR 0.25, 95% CI 0.05 to 0.54). [60] We found no other studies of MMR immunisation, but SSPE is rare where any measles-containing immunisation is in widespread use. Out of 19 brain biopsies of people with SSPE, not one measles virus was linked to an immunisation-like strain [61]

Harms:

Acute fever and febrile seizures:
We found one non-systematic review, [62] one RCT, [63] two retrospective cohort studies, [64] [65] one population-based surveillance programme, [66] and three self-controlled case series assessing fever due to immunisation in otherwise healthy children. [67] [68] [69] The review (search date 1998) of observational studies (number of studies and people not reported) suggested that up to 5% of non-immune people develop moderate-to-high fever (38.6 °C or higher) within 7 to 21 days of immunisation. [62]

The RCT (crossover design) assessed acute adverse effects of MMR compared with placebo in 1162 twins (460 children aged 1 year, of whom 1.3% had previously been immunised; 702 children aged 2 years or more, 95% of whom had previously been immunised or experienced measles). [63] One member of each twin pair was randomly selected and allocated to MMR immunisation followed by placebo 3 weeks later. The remaining twin was allocated to the opposite combination. The RCT found that, among children aged 14 to 18 months, MMR significantly increased the incidence of moderate fever (range 38.6–39.5 °C) within 21 days (25% with MMR *v* 6% with placebo; OR 3.28, 95% CI 2.23 to 4.82) and high fever (>39.5 °C; 7% with MMR *v* 3% with placebo; OR 2.83, 95% CI 1.47 to 5.45) compared with placebo. There was no significant difference among children over 6 years of age in rates of fever between the two groups (5/1000 in children receiving immunisation or placebo; P >0.10) but most had been immunised previously.

The first retrospective cohort study in 679,942 children from four health maintenance organisations (HMOs) in the USA found that children who had received MMR (strains not listed) were significantly more likely to experience febrile seizures 8 to 14 days after receiving MMR compared with children of the same age who had not been immunised (ARI: 25–34 additional seizures/100,000 immunised children; RR 2.83, 95% CI 1.44 to 5.55; ARI estimated by comparison with background seizure risk in all children aged 12–24 months: 0.025%; NNH 4000; CI not reported). [64] The study found no significant difference in febrile seizures during the first week (RR 1.73, 95% CI 0.72 to 4.15) or 15 to 30 days after immunisation (RR 0.97, 95% CI 0.49 to 1.95). The study followed up 562 children with febrile convulsions (22 within 7–21 days of MMR; 18 within 0–7 days of diphtheria, tetanus, and pertussis [DTP]; 1 after both immunisations; and 521 whose seizures occurred outside these periods following immunisation). It found that, when comparing MMR or DTP versus no immunisation, there was no significant difference in the risk of developing subsequent seizures (RR 0.65, 95% CI 0.32 to 1.35). No child with a febrile seizure after immunisation went on to develop afebrile seizures. Similarly, among 273 children with febrile convulsions in one of the four participating HMOs, the study found no evidence that MMR immunisation before seizure significantly increased the risk of learning disability or developmental delay compared with no immunisation before seizure (RR after adjusting for age at first febrile seizure 0.56, 95% CI 0.07 to 4.20). It found no significant increase in afebrile seizures after MMR immunisation (within 15–30 days of MMR: RR 0.48, 95% CI 0.05 to 4.64).

The second retrospective cohort study assessed 537,171 children born in Denmark between 1991 and 1998, of whom 82% (439,251) had received MMR immunisation. [65] It found that, overall, MMR immunisation significantly increased febrile convulsions in the 2 weeks immediately after receiving the immunisation compared with no immunisation, but rates were low in both groups (2.46/1000 children with immunisation *v* 0.90/1000 children with no immunisation; RR 2.75, 95% CI 2.55 to 2.97). Children who had previously had a febrile convulsion, or who had one or more siblings with febrile seizures, were at greatest risk (ARI: children with previous seizures: 19.47, 95% CI 16.05 to 23.55; children with family history of seizures: 3.97, 95% CI 2.90 to 5.40; absolute figures not reported). The study found no significant increase in epilepsy in children who had a febrile convulsion associated with MMR immunisation (RR 0.70, 95% CI 0.33 to 1.50), but found a significant increase in further febrile seizures (RR 1.19, 95% CI 1.01 to 1.41).

The population-based passive surveillance programme assessed harms of MMR in all 1.8 million people immunised over a 14-year period in Finland. [66] Surveillance relied on healthcare personnel's awareness of the programme, and their reporting of adverse events felt to be associated with MMR. Therefore, the results should be treated with caution. Advertisements of the programme appeared in seminars, the media, and the medical press. Acute reactions were more likely to have been reported than long-term effects. Fever was associated with MMR in 277 children (AR: 15/100,000 immunised children or 9.2/100,000 doses). Febrile seizures were reported in 52 children (AR: 17/million doses), 28 of which could have been caused by MMR (9/million doses) according to predefined clinical and serological criteria. These are gross underestimates compared with the US retrospective study, [64] and suggest an inadequacy of the Finnish study for detecting relatively minor events. [66]

The first self-controlled case series examined the incidence of febrile convulsions after immunisation with different MMR strains. [67] In children between 12 and 24 months of age, it found an increased incidence of hospital admission due to febrile seizures 6 to 11 days after receiving any MMR immunisation compared with the control period (AR: 50/100,000; ARI: 33 additional seizures/100,000 doses). From 15 to 35 days after immunisation, there was no increased risk in febrile seizures with Jeryl-Lyn-containing immunisation compared with the control period. However, with the Urabe-containing immunisation, it found an absolute risk of febrile seizures or aseptic meningitis of 91/100,000 immunised children, with an attributable risk of 38/100,000 immunised children compared with control.

The second self-controlled cases series (children aged 12–23 months in North and South Thames regions of England; combined annual birth cohort of approximately 100,000) found a significant increase in febrile convulsions 6 to 11 days after MMR immunisation with immunisations containing either Jeryl-Lynn or RIT 4385 mumps immunisation strains, compared with the preimmunisation control period (relative incidence for immunisations containing Jeryl-Lynn or RIT 4385: 4.09, 95% CI 3.14 to 5.33). [68] However, at 15 to 35 days after immunisation, there was no increase in febrile convulsions compared with the control period (relative incidence for immunisations containing Jeryl-Lynn or RIT 4385: 1.13, 95% CI 0.87 to 1.48).

The third self-controlled case series in the USA (2173 children from one HMO in rural Wisconsin) studied acute adverse effects of MMR in three different groups: children aged 12 to 24 months receiving their first immunisation dose, children aged 4 to 6 years receiving their second immunisation dose, and children aged 10 to 12 years receiving their second immunisation dose. [69] Among toddlers receiving their first immunisation, it found significantly higher rates of fever, rash, and diarrhoea in the 2-week period postimmunisation compared with the 2-week preimmunisation control period (proportion of children reporting at least one symptom of fever, rash, or diarrhoea: 112/535 [21%] preimmunisation *v* 278/535 [52%] postimmunisation; reported as significant; P value not reported). The study found that, in older children receiving their second immunisation dose, there was no significant difference in the incidence of these symptoms during the control period and 2 weeks postimmunisation. [69] These results are broadly consistent with the crossover RCT, [63] although the design of the self-controlled case series is less robust, with no blinding, and parents only recording temperature when a fever was suspected. [69]

Aseptic meningitis:
Observational studies using a variety of methods have reported a wide range of risk estimations for aseptic meningitis after MMR immunisation (AR: 7–250/million immunisations), even in the same country. [70] Using self-controlled case series in the UK, the risk of aseptic meningitis was assessed for MMR immunisations containing either Urabe or Jeryl-Lynn mumps immunisation virus strains. [67] The case series found that the immunisation increased the risk of aseptic meningitis 15 to 35 days after receiving Urabe-containing immunisations (AR: 67/million immunised children; ARI: 63/million immunised children). No cases of aseptic meningitis were reported with the Jeryl-Lynn-containing MMR immunisation. This latter finding was confirmed using similar methods in a US study. [71]

A further self-controlled cases series in the UK (children aged 12–23 months in North and South Thames regions of England; combined annual birth cohort of approximately 100,000) found no cases of aseptic meningitis in the 15- to 35-day period after the administration of an MMR immunisation containing the RIT 4385 mumps immunisation strain (one of the 2 strains found in Jeryl-Lynn immunisations) out of 91,777 doses given. [68]

One retrospective population surveillance study in part of Brazil (based on hospital admissions before and after a mass immunisation campaign using Urabe-containing MMR) found that MMR significantly increased the risk of aseptic meningitis 3 to 5 weeks after immunisation (32/452,344 doses; RR 30.4, 95% CI 11.5 to 80.8; attributable risk 71/million doses). [72] A case crossover study of hospitalised children found no significant risk of developing aseptic meningitis with the Jeryl-Lynn or the Rubini strains of the immunisation (RR 0.60, 95% CI 0.18 to 1.97). It found an increased risk after immunisation with the Urabe or Hoshino strains, particularly in the third week after immunisation (RR 15.6, 95% CI 5.9 to 41.2). [73] However, the assignment of immunisation strains was based on assuming a pattern of provider usage rather than individual records, and there was no evidence that this assumption was tested. Reported cases of aseptic meningitis increased during a mass MMR immunisation campaign using the Leningrad–Zagreb mumps strain in Brazil in 1997, compared with the previous 2 years (28.7 cases/10,000 person-weeks *v* 4.5 cases/10,000 person-weeks). [74] The absolute risk of aseptic meningitis 15 to 35 days after immunisation was 29/100,000 doses. Other causes of aseptic meningitis were not ruled out and therefore the attributable risk could not be calculated, but the temporal pattern of increase in cases suggests that most were due to the immunisation. The risk of aseptic meningitis following Leningrad–Zagreb-containing MMR seems higher than that following both Urabe- and Jeryl-Lynn-containing immunisations. Similar findings were reported after a mass immunisation campaign with Leningrad–Zagreb immunisation in two states in Brazil in 1998. [75] The incidence of aseptic meningitis increased compared with the previous 2 years. The estimated attributable risk of aseptic meningitis after immunisation ranged from 52 per million to 160 per million immunisations, depending on the criteria used.

Idiopathic thrombocytopenic purpura (ITP):
Naturally acquired measles and measles immunisation have both been associated with ITP. We found three self-controlled case series, [67] [76] [77] the second including the cases from the first, and one case control study. [78] In these studies, immunisation records were linked with computerised hospital admission records, and the incidence of ITP during a risk period (0–42 days after MMR immunisation) was compared with the incidence outside this risk period.

The first two studies found a significant increase in incidence of ITP after MMR immunisation (AR: 45/million people; ARI: 31/million people; RR 3.27, 95% CI 1.49 to 7.16). [67] [76] The study included 14 children who had had a first episode of ITP before MMR immunisation. Although three of these children had further episodes of ITP, none were within 6 weeks of immunisation.

The third self-controlled case series of children in south-east England also found an increased incidence of ITP in the 4-week risk period after MMR immunisation compared with the preimmunisation control period (6 cases in risk period; number of immunisation doses not reported; relative incidence 6.91, 95% CI 1.81 to 26.4). [77]

The case control study carried out in the UK found that MMR was associated with an increased incidence of ITP within 6 weeks of immunisation (ARI: 40/million immunised children, 95% CI 11/million to 47/million). [78]

Arthritis and arthralgia:
One crossover RCT in twin children found that immunisation with MMR, given either at 14 to 18 months of age, or at 6 years of age, significantly increased the risk of developing arthralgia compared with placebo (14–18 months: OR 3.66, CI 1.74 to 7.70; P <0.001). [63] The duration of arthralgia was not described, but it is implied that it was mild.

Anaphylaxis:
Anaphylaxis after MMR has been reported, albeit infrequently. [79] We found no accurate figures. During the 1994 measles–rubella immunisation campaign in the UK, 5.8 million children (aged 5–16 years) were immunised. A passive surveillance using "yellow cards" identified 123 reports of children with signs or symptoms of allergic reactions in varying degrees of severity, but with no deaths or anaphylaxis within 24 hours of immunisation. [80] The absolute risk is therefore 15/million doses. If confined to anaphylactic reactions, the rate was 1/100,000 doses. [81]

Asthma and eczema:
We found one systematic review, [82] three cohort studies [83] [84] [85] and two case control studies. [86] [87] The systematic review found three studies relating to measles immunisation and one to MMR, all of which had limitations to the methods used, precluding the possibility of drawing an overall conclusion. [82]

The cohort studies, all of which had weak methods, found no evidence of an association between MMR and asthma or eczema. The first cohort study in four HMOs in the USA compared the MMR immunisation status of children with diagnosed and treated asthma. [83] Inclusion criteria were children with asthma after the age of 1 year who had been enrolled with the HMO at birth, and remained so until at least 18 months of age. The median age at last follow-up for the whole group of children was 28 months. The median age at first episode of asthma was 11 months. It found that the risk of developing asthma was not increased after MMR immunisation (RR 0.97, 95% CI 0.91 to 1.04). It found no change in these figures when only those children with asthma requiring emergency department attendance or hospital admission were included. Although the duration of follow-up was relatively short (28 months), the authors argue that this was probably long enough to pick up most cases. [83]

The second cohort study, carried out in the USA, assessed children who had been enrolled in an earlier case control study of infant wheezing, and compared the incidence of asthma in children with MMR immunisation versus non-immunised children. [84] It included 1778 children aged 3 to 7 years, of whom 881 had wheezed in infancy and 897 had not. The study found no significant difference in the proportion of children who had asthma between immunised and non-immunised children (33/383 [9%] of immunised children *v* 125/1395 [9%] of non-immunised children; adjusted OR 1.19, 95% CI 0.78 to 1.82). Secondary analysis also found no significant difference in the incidence of asthma between immunised and non-immunised children with a history of infant wheezing (adjusted OR 1.20, 95% CI 0.55 to 2.63), or with no history of infant wheezing (adjusted OR 1.05, 95% CI 0.65 to 1.70; absolute numbers not reported).

The third cohort study, using the General Practice Research Database (GPRD) in the UK (29,238 children) assessed the incidence of asthma/wheeze and eczema following MMR immunisation. [85] Only children without asthma, wheeze, or eczema before immunisation were included. The study found a significant increase in the risk of asthma and eczema after MMR immunisation (asthma: 1753/16,470 children immunised over 69,602 person-years, adjusted HR 2.20, 95% CI 1.50 to 3.21; eczema: 1884/14,353 children over 59,520 person-years, adjusted HR 3.50, 95% CI 2.38 to 5.15). The difference between the groups in asthma incidence was only evident in children who consulted their doctor less frequently. This raises the possibility that some of the children within this very small group may have had undiagnosed asthma. Furthermore, only 1.6% of children in the study were non-immunised, which makes the results difficult to interpret.

The first case control study carried out in New Zealand in children aged 7 to 9 years, who were diagnosed with asthma (233 cases; 241 controls), found no significant association between MMR immunisation and diagnosed asthma (OR 1.43, 95% CI 0.85 to 2.41). [86] The authors of this report concluded that there may be some underdiagnosis of children with asthma.

The second case control study, conducted using two separate primary care databases in the UK (the GPRD and the Doctors' Independent Network database), compared rates of immunisation with the MMR and DTP immunisations in children with hay fever with rates in matched controls. [87] Children identified from the GPRD database (4196 pairs) were equally likely to develop hay fever whether or not they had been immunised with MMR, and the age at immunisation was unimportant. However, there were some differences in the Doctors' Independent Network database (2902 pairs). When the two were combined, the only significant finding was that children who had their first MMR immunisation at over 24 months of age were less likely to develop hay fever compared with children first immunised by 14 months of age (7098 pairs, adjusted OR 0.67, 95% CI 0.52 to 0.90; P = 0.007). Children who were not immunised with MMR were not at significantly lower risk of developing hay fever than those immunised at 14 months old (OR 0.82, 95% CI 0.59 to 1.12).

Diabetes mellitus:
We found one population-based study of children born in Denmark between 1990 and 2000, which used hospital records (initially inpatient only, and then all hospital attendances) to calculate the number of children who developed type 1 diabetes mellitus, and compared the incidence of diabetes between immunised and non-immunised children. [88] The authors stated that the use of hospital records would account for over 90% of children with diabetes in Denmark. They found that 681 children out of 739,694 enrolled (4,720,517 person-years) had type 1 diabetes. The study found no significant difference in the incidence of diabetes between children who had received MMR and those who had not (RR 1.14, 95% CI 0.90 to 1.45).

Guillain–Barré syndrome:
Guillain–Barré syndrome has been reported after immunisation with measles-containing immunisations. [62] In the 1994 to 1995 measles–rubella campaign in the UK, three cases of Guillain–Barré syndrome were reported, but this is well within the expected background rate. [80] A retrospective study of Finnish hospital discharges in people who developed Guillain–Barré syndrome looked at immunisation records over a 4-year period and found no cases of Guillain–Barré syndrome within 6 weeks of immunisation. [66] The shortest interval was 10 weeks, and was in a person who also suffered an infectious illness during this interval.

Gait disturbance:
We found one retrospective review [89] of adverse effects notification forms received in Denmark between 1987 and 1996 and one self-controlled case series undertaken in the UK. [90] The review suggested that gait disturbance followed MMR immunisation in a small number of children (about 8 cases/100,000 doses of MMR). [89] The self-controlled case series (62 children aged 12–24 months) used hospital admission data in the UK to assess the risk of gait disturbance requiring admission to hospital within 60 days of MMR immunisation. [90] It found no significant increase in the incidence of gait disturbance requiring admission to hospital at 6 to 60 days after MMR immunisation (RR 0.46, 95% CI 0.16 to 1.35).

Demyelinating disease:
We found one multicentre case control study undertaken in adults from HMOs in the USA (332 people aged 18–49 years with multiple sclerosis: 772 controls; 108 people with optic neuritis: 228 controls), assessing a possible association between MMR immunisation and the development of central nervous system demyelinating disease. [91] It found no significant increase in multiple sclerosis or optic neuritis in people who had received MMR immunisation (multiple sclerosis: OR 0.9, 95% CI 0.4 to 1.9; optic neuritis: OR 0.8, 95% CI 0.3 to 2.2).

Developmental regression or autistic spectrum disorders:
We found one non-systematic review of observational studies, [92] one case control study (624 cases of autistic spectrum disorders), [93] one large retrospective cohort study (738 cases of autistic spectrum disorders), [94] and four additional population surveillance studies (498 cases of autistic spectrum disorders analysed in two studies; [95] [96] 278 cases of autistic spectrum disorder in a total birth cohort of 31,426; [97] and an estimated total population of 1.8 million immunised people in a further study). [66] None of the studies found an association between the MMR immunisation and autistic spectrum disorders.

The non-systematic review (search date not reported) found no causal relationship between MMR and autism. [92] The review included two large cross-sectional time series, [98] [99] reporting that the incidence of autism increased independently of MMR coverage. They found no association between MMR immunisation and autism. The first cross-sectional time series was carried out among kindergarten children in California in 1999. [98] It looked at children born between 1980 and 1994 and immunised with MMR by 17 or 24 months, and compared these figures with autism cases referred to the state developmental services department over the same time period (absolute figures not reported). It found that MMR coverage at 24 months rose slightly (from 72% in 1980 to 82% in 1994; 14% proportional rise). Referral rates for new autism cases increased disproportionately in the same period (from 44/100,000 live births in 1980 to 208/100,000 live births in 1994; a 373% proportional rise). The authors of the report found it difficult to attribute the large increase in referral rates to the small rise in immunisation rates. However, referral rates to the department may not reflect accurately the incidence of autistic syndromes.

The second cross-sectional time series was carried out in the UK. [99] It found that, during the period between 1988 and 1993, the risk of autism among boys increased, whereas MMR coverage remained almost constant at about 97% (AR of first diagnosis of autism aged 2–5 years: 8/100,000, 95% CI 4/100,000 to 14/100,000 for children born in 1988 *v* 29/100,000, 95% CI 20/100,000 to 43/100,000 for children born in 1993; 305 cases of autism over approximately 3 million person-years at risk). [99]

The case control study (624 children with autism aged 3–10 years and 1824 age-, sex-, and school-/region-matched controls) also found no significant association between measles immunisation and autism (immunisation before 18 months: 70.5% for cases *v* 67.5% for controls; OR 1.12, 95% CI 0.91 to 1.38). [93] The study assessed immunisation at certain ages and compared rates of autism in immunised children with those in healthy, but not immunised, controls. MMR immunisation was divided into: "on time" immunisation (before 18 months of age) compared with no immunisation by this age; MMR immunisation before 24 months of age compared with no immunisation; and immunisation before 36 months of age compared with no immunisation. Only the latter analysis was significant (93% of children with autism immunised at 36 months *v* 91% of control children; OR 1.49, 95% CI 1.04 to 2.14). In practice, most children receive MMR immunisation by the age of 2 or 3 years. The apparent increase in the risk of autism in the analysis at 36 months is thought to be an artefact resulting from the requirement for MMR immunisation of autistic children before entering special education programmes at the age of 36 months. Non-autistic children not immunised before the age of 2 or 3 years will generally not be immunised until they enrol in school at around 5 years of age.

The large retrospective cohort study (537,303 children born in Denmark between January 1991 and December 1998; 2,129,864 person-years' exposure) found no association between MMR immunisation and autistic spectrum disorders (82% of population immunised; RR of autistic disorder in immunised *v* non-immunised children 0.92, 95% CI 0.68 to 1.24; RR of other autistic spectrum disorder in immunised *v* non-immunised children 0.83, 95% CI 0.65 to 1.07). [94] It also found no association between autistic spectrum disorder and age at time of immunisation (P = 0.23), time since immunisation (P = 0.42), or calendar date of immunisation (P = 0.06). Results remained unchanged when children with autistic disorders owing to fragile X syndrome, tuberous sclerosis, congenital rubella syndrome, or Angelman's syndrome were included. However, it is possible that the young age of some children at the close of the study may have biased the results against an association. It is not possible to ascertain from the published data whether this potential bias was allowed for.

The first population surveillance study used records at child development centres and special schools to identify 498 children diagnosed with autism before the age of 5 years born in eight health districts in the UK between 1979 and 1998. [95] It found that the incidence of autism increased over this period. However, there was no change in the rate after the start of the MMR immunisation programme. Using the same methods and birth cohort, but including fewer districts (473 children diagnosed with autism before the age of 5 years), the proportion of children with autism who had developmental regression or bowel symptoms was assessed. [96] The study found no significant increase in these conditions during this time period (P = 0.50 for developmental regression and P = 0.47 for bowel symptoms).

The second long-term population surveillance study from Finland was based on passive reporting, and found no cases of immunisation-related developmental regression among 1.8 million people immunised with MMR. [66] However, events that did not result in hospital admission or were not temporally closely associated with the immunisation may not have been reported in this study. This would particularly apply to conditions such as autism, and so it is not possible to draw any conclusions from this study about a possible link between MMR and autism spectrum disorders in either the long or the short term.

A population study of children (total birth cohort 31,426) in Kohuko Ward in Japan examined the numbers of children diagnosed with autistic spectrum disorder before and after changes to the recommendations for MMR immunisation. [97] In the initial period, the combined immunisation was recommended for all children at 1 year of age, but uptake diminished from 70% in babies born in 1988, to 2% in those born in 1992. From 1993, separate measles and rubella immunisations were recommended, and mumps immunisation became voluntary. It was intended that at least 4 weeks should be left between each immunisation. Approximately 90% of children have a routine health check at 18 months of age, which includes a screen for autism. At 3 years, a further health check, including a screen for autism, is offered. The incidence of autism continued to rise, from 48 (95% CI 25.0 to 71) per 10,000 children born in 1988 to 117.2 (95% CI 80 to 156) per 10,000 children born in 1996, despite this change in practice. The study found that the incidence of definite or probable autism with regression did not change significantly over the study duration. The main limitation of this study is that immunisation practice, as opposed to policy, is not recorded, either for the total population or for those children with autistic spectrum disorder. The investigators did not ascertain the immunisation status of the children diagnosed with autistic spectrum disorders, and also did not report figures for the uptake of monovalent immunisations in the general population. However, these flaws are unlikely to be sufficient to negate the conclusion that the combined MMR immunisation is not responsible for the rise in prevalence of autistic spectrum disorder.

Inflammatory bowel disease:
We found one non-systematic review, [62] one cohort study, [100] one population surveillance study, [66] one case control study, [101] and one case series. [102] None of the studies found an association between MMR and inflammatory bowel disease.

The non-systematic review (search date 1998; 6 large observational studies from different resource-rich countries) found no evidence of an association between inflammatory bowel disease and measles immunisation (meta-analysis not performed). [62]

The retrospective cohort study compared rates of ulcerative colitis, Crohn's disease, and inflammatory bowel disease (assessed by postal questionnaire) in 7616 people who had received live monovalent measles immunisation with rates in people who had not received measles immunisation by the age of 5 years (mean age at immunisation: 17.6 months; standard deviation 7.4 months). [100] Participants were those available from an original population-based cohort of all 16,000 children born in the first week of 1970 in the UK. The study found no significant difference in the risk of developing ulcerative colitis, Crohn's disease, or inflammatory bowel disease among people (aged 26 years at the time of the study) who had received monovalent measles immunisation and those who had not, whether or not the result was adjusted for sex, socioeconomic status, or crowding (AR for Crohn's disease: 0.25% with immunisation *v* 0.31% without immunisation; adjusted OR 0.7, 95% CI 0.3 to 1.6; AR for ulcerative colitis: 0.16% with immunisation *v* 0.27% without immunisation; adjusted OR 0.6, 95% CI 0.2 to 1.6; AR for inflammatory bowel disease: 0.41% with immunisation *v* 0.58% without immunisation; adjusted OR 0.6, 95% CI 0.3 to 1.2).

The long-term population-based passive surveillance study from Finland found no cases of inflammatory bowel disease associated with immunisation in 1.8 million people immunised with MMR who were followed up for 14 years, but there are major limitations to the methods used in this study. [66]

The case control study included 142 people in the USA with definite or probable inflammatory bowel disease from members of four HMOs (67 people with ulcerative colitis and 75 people with Crohn's disease). [101] Cases (people with inflammatory bowel disease) were identified by computerised search of electronic records and manual abstraction of medical records from 1958 to 1989 for three HMOs, and from 1979 to 1989 for the remaining one. The date of data collection is not clear, and the potential age range was not reported; people who were not members of the HMO between 6 months of age and disease onset were excluded. The study found that people with inflammatory bowel disease were no more likely to have received MMR than people without inflammatory bowel disease taken from the same HMO and matched for sex and year of birth (Crohn's disease: OR 0.40, 95% CI 0.08 to 2.00; ulcerative colitis: OR 0.80, 95% CI 0.18 to 3.56; all inflammatory bowel disease: OR 0.59, 95% CI 0.21 to 1.69). [101] The study similarly found no association between other measles-containing immunisations and Crohn's disease, ulcerative colitis, or all inflammatory bowel disease. The analysis in the paper compared MMR or other measles-containing immunisations versus no measles-containing immunisation. The other measles-containing immunisations are almost certain to be the single measles immunisation, but this was not made explicit in the paper, so it is inappropriate to comment further. The case series raised the question of a possible relationship between MMR and developmental regression in 12 children with bowel symptoms. [102] The series was retrospective (parents surveyed up to 8 years after immunisation), small, lacked a control group, and was selective in its sample. The authors stated that it does not prove a link or causal association between MMR immunisation and their postulated syndrome of autism and enterocolitis.

Leukaemia:
We found two case control studies examining a possible link between childhood immunisations and the development of leukaemia. [103] [104] The first study of children with acute leukaemia found that they had no significantly higher likelihood of having received MMR immunisation (measured as number of doses administered) compared with controls (323 children plus 409 matched controls; OR 1.06, 95% CI 0.69 to 1.63). [103] This is in keeping with the second case control study, [104] which also found no significantly higher rates of MMR immunisation in children who had acute lymphoblastic leukaemia (RR 1.19, 95% CI 0.67 to 2.10).

Non-targeted infections:
We found one self-controlled case series [105] and one population-based study. [106] For the case series, details of MMR immunisation were ascertained for 387 children, aged 12 to 23 months, admitted to hospital with a diagnosis of invasive bacterial infections or lobar pneumonia. Children with a known underlying susceptibility to bacterial infection were excluded. There was no increase in admissions in any of the three 30-day periods up to 90 days after immunisation. The odds ratio for the whole 90-day period was 0.76 (95% CI 0.58 to 0.99). [105]

The population-based study, conducted from 1990 to 2001 in Denmark, where MMR immunisation is usually given at 15 months of age, collected data on hospital admissions in children under 5 years old, due to non-immunisation preventable infections. There were 84,317 such admissions in 805,206 children, with 2,900,463 person-years of follow-up. The study reported slightly higher admission rates for upper respiratory tract infections within 14 days of MMR immunisation compared with non-immunised children (RR 1.1, 95% CI 1.01 to 1.21). However, there was no significant difference in admission rates for viral or bacterial pneumonia, diarrhoea, viral central nervous system infection, bacterial meningitis, or septicaemia in the 14 days after MMR immunisation, and no overall significant increase in admissions for any infection in immunised children compared with non-immunised children (data presented graphically). [106]

Comment: A systematic review [107] considered both the effectiveness and unintended effects associated with MMR immunisation. The reviewers identified RCTs and observational studies, but no meta-analyses or data syntheses were performed because the studies identified used different outcomes, which were often poorly defined, and had different time spans. The studies were generally considered to have used flawed methods. When those studies with the lowest risk of systematic error alone were considered, there appeared to be a reduction in upper respiratory tract infections, but an increase in febrile convulsions in the first 2 weeks after MMR immunisation compared with no immunisation or placebo. However, these studies found no evidence of an increase in aseptic meningitis with the Jeryl-Lynn-strain mumps immunisation, and no evidence of a causal association between MMR immunisation and Crohn's disease, ulcerative colitis, or autism. The review was unable to identify any studies assessing the effectiveness of MMR that fulfilled the review's inclusion criteria. We consider that the inclusion criteria were too limited; for example, only studies comparing MMR with no immunisation or placebo were included for effectiveness, many studies were criticised for not stating exactly which brand of MMR was used, and an early self-controlled case series [108] was excluded.

We have included many of the excluded articles in our discussion. The excluded self-controlled case series used linked immunisation and hospital admission data for 1285 children aged 12 to 24 months admitted with febrile convulsions, non-bacterial meningitis, or idiopathic thrombocytopenic purpura in five district health authorities in England. The study found an absolute attributable risk of febrile convulsions 6 to 11 days after immunisation of 1 per 3000 doses, an increased risk of febrile convulsions 15 to 35 days after immunisation only with the Urabe mumps immunisation, and an increased risk of idiopathic thrombocytopenic purpura 15 to 35 days after immunisation at a rate of 1 per 24,000 doses of MMR immunisation. [108]

Benefits:
RCTs comparing the clinical effects of MMR or monovalent immunisation versus no immunisation or placebo are now deemed unethical because of the existing evidence of the high protective efficacy of measles-containing immunisations, and the harms associated with naturally acquired measles, mumps, and rubella.

Cohort studies of measles antibody levels after MMR or monovalent measles immunisation:
One prospective cohort study (621 children from 1 HMO in rural Wisconsin, USA) followed two groups of children: those who received their second dose of MMR immunisation aged 4 to 6 (MMR1), and those who received their second dose aged 10 to 12 years old (MMR2). [109] The intention was to observe the pattern of antibody levels over the time, in the absence of natural boosting, so children who lived in a household with a case of measles, mumps, or rubella were excluded, as were those who were immunosuppressed.

The study reported that 154/312 children in the MMR1 group and 210/319 children in the MMR2 group were followed up and had blood taken at 15 years of age — 10 years after immunisation for MMR1 and 5 years after immunisation for MMR2 — as well as at younger ages. No child was seronegative (measles antibodies of <8 mIU/mL) at follow-up; however, at 15 years of age, nine children in each group had low antibody levels (8–120 mIU/mL), indicating susceptibility to infection. At 15 years of age, there was no significant difference in the geometric mean titres (GMT) between the two groups (641 mIU/mL in MMR1 *v* 737 mIU/mL in MMR2; P = 0.29). There was a trend for antibody levels to fall, and the authors suggested that the proportion potentially susceptible to measles would reach 33% by 20 years after MMR2, but the proportion seronegative (GMT

<8 mIU/mL) would not reach 1% until 30 years after MMR2. [109] Follow-up rates in this study were low, with only 59% of children enrolled returning for their second blood sample at age 15 years.

Population-based studies of measles mortality after MMR or monovalent measles immunisation:
We found one low-quality systematic review (search date not reported; 10 retrospective cohort studies; 2 case control studies), which found that live monovalent measles immunisation in seven resource-poor countries reduced all-cause mortality in immunised children by 30% to 80% compared with non-immunised children, depending on follow-up period and country. [110] However, the results of the review should be interpreted with caution. The review included studies that did not account for potential confounders between immunised and non-immunised groups, such as age, sex, area, and literacy. The review attempted to adjust for selection bias of immunised children (who would potentially receive better health care) by looking at DTP immunisation status. However, this was documented in only a limited number of studies. Immunisation efficacy rates were only significant in five studies that looked at immunised and non-immunised children in the same community (efficacy 40–86%). [110]

Harms:
Results of studies assessing fever in children immunised against measles should be interpreted in light of the very high prevalence of acute fever in children with measles infection. [63] [111] [112] A large proportion of the literature on adverse events after immunisation is based on passive reporting, albeit enhanced. [66] This has major limitations. Events may be under-reported, and yet events that are reported may not be linked to the intervention. For example, a case series postulated a possible causal association between MMR and a syndrome of autism and enterocolitis, despite no evidence being found to prove this association. [102] Such studies can flag up issues for further investigation, but cannot be used as definitive evidence either of size of risk or even causal association, because they are only generating hypothesis.

Clinical guide:
The use of MMR rather than monovalent measles, mumps, and rubella immunisations provides earlier protection against all three diseases. Use of single immunisations also requires more injections over a longer period of time, which may lower uptake rates. Decreased use of MMR immunisation leads to a concomitant increase in the pool of individuals susceptible to measles, mumps, and rubella in the community. This results in an increase in transmission of the respective viruses and, therefore, a higher prevalence of all three diseases and their resulting complications. There is less evidence on the safety and efficacy of the immunisations given in a staged manner during early childhood than there is for the combined MMR.

OPTION MMR VERSUS MONOVALENT MEASLES IMMUNISATION

Treatment effectiveness (clinical cases; rates of seroconversion)
MMR compared with monovalent measles immunisation We found insufficient evidence from three RCTs on whether MMR and monovalent measles immunisation differ in effectiveness in increasing seroconversion rates. We found no evidence comparing the clinical effects of MMR and monovalent measles immunisation.

Benefits: We found no systematic review or RCTs comparing the clinical effects of MMR versus monovalent immunisation. We found three RCTs comparing rates of measles seroconversion after live MMR (Schwarz measles plus Urabe Am9 mumps plus RA 27/3 rubella) versus Schwarz-strain monovalent measles immunisation. [112] [113] [114] The first RCT (420 children with no clinical history of measles or mumps; mean age about 15 months) found similar seroconversion rates in both groups after 6 weeks (93% with MMR *v* 97% with monovalent immunisation). [112] The second RCT (319 children; mean age 13 months) also found similar seroconversion rates in both groups at 6 weeks (93% with MMR *v* 92% with Schwarz-strain monovalent measles immunisation). [113] The third RCT (502 children aged 15 months–4 years) also assessed seroconversion rates. It compared seven interventions: monovalent measles (Moraten strain); monovalent mumps (Jeryl-Lynn strain); monovalent rubella (RA 27/3 strain); monovalent rubella (HPV-77:DE-5 strain); MMR containing Moraten measles plus Jeryl-Lynn mumps plus RA 27/3 rubella; MMR containing Moraten measles plus Jeryl-Lynn mumps plus HPV-77:DE-5 rubella; and placebo. The RCT found similar measles seroconversion rates with monovalent measles immunisation and both MMR immunisations (99% with either MMR *v* 100% with monovalent immunisation; significance assessment not reported). [114]

Harms: The first RCT found no significant difference in the proportion of children with fever between MMR and monovalent measles immunisation (38% with MMR *v* 38% with monovalent immunisation; $P > 0.05$). [112] In the second RCT, there were similar rates of fever (34% with MMR *v* 29% with monovalent immunisation; significance assessment not reported), irritability (67% with MMR *v* 71% with monovalent immunisation; significance assessment not reported), and rash (41% in both groups; significance assessment not reported) between MMR and monovalent immunisation up to 3 weeks after immunisation. Both MMR and monovalent immunisation were associated with lymphadenopathy (2% with MMR *v* 1% with monovalent immunisation; significance assessment not reported), and 1% of children who received MMR had parotitis compared with none who received monovalent immunisation. [113] The third RCT assessed adverse effects in children with seroconversion, and found that a similar proportion of children receiving monovalent measles and either MMR had fever (36% with MMR containing rubella RA 27/3 *v* 30% with MMR containing rubella HPV-77:DE-5 *v* 33% with monovalent immunisation; significance assessment not reported). [114] Rates of local reactions, rash, respiratory symptoms, lymphadenopathy, and sore eyes tended to be higher with MMR immunisations. All RCTs are likely to have been underpowered to detect other clinically important adverse effects.

We found two observational studies comparing the incidence of autism following monovalent measles immunisation versus MMR. [115] [116] Both studies had flaws in their methods, meaning we were unable to draw conclusions about the effects of monovalent or MMR immunisations on the risk of autism. The case control study included small numbers (21 cases and 42 controls) and there was a low response rate from the parents of children in the control group (58%), which may have led to bias. [115] The other observational study recruited members of a parent's organisation, and conducted a time-trend analysis in people with autism aged 6 to 40 years. [116] The analysis was made at a single point in time, regardless of the age of the participants. It is likely that the characteristics of the older members of the group would be different from the younger ones, which makes a time-trend analysis difficult to interpret. The inclusion of a self-selected group of people also makes the results subject to bias.

Comment: The third RCT compared monovalent measles, mumps, and rubella immunisations versus the MMR, and is reported separately in all relevant options. [114]

Measles risk after seroconversion:
One systematic review (search date 1995; 6 cohort studies of live immunisation) examined risk of measles infection at least 21 days after immunisation-induced seroconversion (monovalent or polyvalent immunisation). [117] When cross-checking immunisation status against medical records, it found that the incidence of clinical measles infection in children who had seroconverted after immunisation was zero (0 infections from 2061 people exposed; 0%, 95% CI 0% to 0.147%).

QUESTION What are the effects of mumps immunisation?

OPTION MONOVALENT MUMPS IMMUNISATION OR COMBINED MMR IMMUNISATION

Treatment effectiveness (clinical cases; rates of seroconversion)
Compared with placebo or no immunisation Two RCTs, observational studies, and several population-based studies found consistent evidence that mumps immunisation (MMR or monovalent) reduced the incidence of mumps infection.

Adverse effects
Compared with placebo or no immunisation One RCT, cohort studies, and population-based studies have found that MMR immunisation was associated with increased rates of fever and febrile seizures, although febrile seizures were rare, and there was no evidence of increased rates of afebrile seizures. Observational studies found that MMR containing some immunisation virus strains was associated with an increased risk of aseptic meningitis, and MMR immunisation was also associated with an increased risk of idiopathic thrombocytopenic purpura and arthralgia. Observational studies found no evidence of an association between MMR immunisation and the risks of developing asthma, type 1 diabetes, Guillain–Barré syndrome, gait disturbance, multiple sclerosis, optic neuritis, autism or autistic spectrum disorders, leukaemia, or inflammatory bowel disease. Anaphylaxis has been reported after immunisation with MMR, but this is rare.

Note:
RCTs using a control group receiving no immunisation or placebo are now deemed unethical because of the existing evidence of the efficacy of MMR, and because of the potential harms associated with naturally acquired measles, mumps, or rubella infection. Mumps can cause neurological problems and hearing loss, orchitis, and pancreatitis.

Benefits: **RCTs of mumps incidence after MMR or monovalent immunisation:**
We found no systematic review. We found no RCTs comparing the clinical effects of MMR versus no immunisation or placebo. We found two RCTs comparing monovalent mumps immunisation versus placebo, reported in four papers. [118] [119] [120] [121] Both RCTs found that monovalent mumps immunisation reduced the incidence of mumps. The first RCT (open-label design; conducted in the USA in 1965) followed 3924 children for 5 months. [118] [119] Children were allocated to live immunisation (Jeryl-Lynn strain; 2965 children) or saline (329 children). The RCT found that mumps incidence was about 21 to 23 times greater in children receiving placebo than in immunised children. Immunisation efficacy was estimated to be 96% during this time. However, the number of immunised

and non-immunised children at risk of developing mumps was estimated by extrapolation of serological data from the study, rather than by observation of development of disease. [118] [119]

The second RCT (conducted between 1965 and 1966 in the USA) followed 867 children for 5 to 9 months. [120] [121] Children were allocated to live immunisation (Jeryl-Lynn strain; 362 children) or no immunisation (505 children). The RCT found that mumps incidence was much lower in immunised compared with non-immunised children (2% with mumps immunisation *v* 61% with no immunisation; significance not assessed). [120] Immunisation protective efficacy was 97%. When the study duration was extended and the study population included families and contacts, the overall protective efficacy of mumps immunisation was at least 95%.

Population-based studies of mumps incidence after MMR or monovalent immunisation:
There are numerous population-based studies evaluating the effects of MMR immunisation on mumps incidence, and we report four representative studies from the UK and the USA below. [122] [123] [124] [125] A population-based surveillance report from the USA showed a 99% reduction in cases of mumps in 1993 compared with 1968, when the mumps immunisation was first licensed. [122] Similarly, a population-based surveillance study in the UK found that, following the introduction of MMR into the routine childhood immunisation schedule in 1988, mumps cases decreased by 79% over 2 years. [123] In subsequent years, mumps incidence reduced further, with a 92% reduction in hospital admissions related to mumps. [124] However, the number of confirmed mumps cases increased to about 8000 cases in 2004, compared with 3907 cases in the previous 5 years. [125] This was predicted by seroprevalence studies in 1993, which showed that certain cohorts remained susceptible to mumps infection because they were less likely to have been exposed to natural infection (following high uptake of MMR when routine immunisation began). [124] [125] Those considered to be at particularly high risk of developing mumps were people who were too old to have received two doses of MMR in the routine schedule, and people too young to have been exposed to natural infection. Confirmed cases have been mainly in older teenagers and young adults (born between 1982 and 1990). [125]

Outbreak analyses of mumps incidence after MMR or monovalent immunisation:
Outbreak studies have found lower mumps immunisation efficacy than reported by RCTs. [126] [127] For example, we found one case control study (188 cases; 245 controls; assessed using provider verified records) undertaken during a 1986 outbreak of mumps in Tennessee, USA. [126] It found that overall mumps immunisation efficacy was 74% (95% CI 5% to 84%). [126] The type of immunisation used was not specified, although MMR was widely available in the USA at this time. Another case control study (161 cases; 192 controls; undertaken during the 1998 to 1999 outbreak of mumps in the UK) found that 50% of the identified cases and 77% of the controls had a history of at least one MMR immunisation. Immunisation effectiveness of any MMR immunisation adjusted for age, sex, and general practice was 69% (95% CI 41% to 84%). [127] Outbreak studies may underestimate immunisation effectiveness, because disease transmission rates during the outbreak may be higher than those in the general population. However, immunisation failure may also account for the lower efficacy rates seen in some of these analyses.

Studies of mortality after MMR or monovalent immunisation:
We found no studies assessing mortality due to mumps in children who had received MMR or monovalent immunisation. Mortality due to mumps is rare and it would require large studies to detect an effect.

Harms: For harms of MMR immunisation see monovalent measles immunisation or combined MMR immunisation versus placebo or no immunisation, p 4 .

Comment: RCTs comparing the clinical effects of MMR immunisation versus no immunisation or placebo are deemed unethical because of the existing evidence of the high protective efficacy of the MMR immunisation and the harms associated with naturally acquired measles, mumps, and rubella. It is unclear whether all strains of mumps immunisation have equivalent immunisation efficacy.

Comparative efficacy of strains of mumps immunisation:
An outbreak study in Singapore (5072 children; 4145 immunised; 614 non-immunised; and 313 unknown immunisation status) found that the overall attack rate was 4.8% in the immunised group compared with 5.7% in the non-immunised group. [128] When different strains of mumps immunisation were compared, the immunisation efficacy of the Jeryl-Lynn strain was greater than for the Urabe strain, whereas the Rubini strain did not seem to offer any protection against mumps infection (Jeryl-Lynn: 711 children with 8 cases of mumps, immunisation efficacy 80.7%; Urabe: 190 children with 5 cases of mumps, immunisation efficacy 54.4%; Rubini: 1694 children with 150 cases of mumps, immunisation efficacy –55.3%, 95% CI –121.8% to –8.8%; other confidence intervals or P values not reported). A total of 235 children developed mumps in this outbreak, 200 of whom had been previously immunised. However, it should be noted that the strain of immunisation was

not documented in 1550/4145 (37%) of the immunised children. There were 614 non-immunised children, 35 of whom had mumps. [128] We have not systematically searched for studies assessing the comparative efficacy of different mumps immunisation strains. However, the Rubini strain of mumps immunisation was widely used throughout Asian countries, Switzerland, Spain, and Italy in the 1990s, and is still in use in some countries, but to a lesser extent.

OPTION MMR VERSUS MONOVALENT MUMPS IMMUNISATION

Treatment effectiveness (clinical cases; rates of seroconversion)
MMR compared with monovalent mumps immunisation We found insufficient evidence from one RCT on whether MMR and monovalent mumps immunisation differ in effectiveness in increasing seroconversion rates. We found no evidence comparing the clinical effects of MMR and monovalent mumps immunisation.

Benefits: We found no systematic review or RCTs comparing the clinical effects of MMR versus monovalent immunisation. We found one RCT (502 children aged 15 months to 4 years) comparing seroconversion rates of monovalent measles (Moraten strain), monovalent mumps (Jeryl-Lynn strain), or monovalent rubella (both RA 27/3 and HPV-77:DE-5 strains) versus seroconversion rates of their trivalent MMR counterparts (MMR containing Moraten measles plus Jeryl-Lynn mumps plus RA 27/3 rubella or MMR containing Moraten measles plus Jeryl-Lynn mumps plus HPV-77:DE-5 rubella). [114] The RCT found similar mumps seroconversion rates with monovalent mumps immunisation and both MMR immunisation (89% with monovalent mumps *v* 89% with MMR containing rubella RA 27/3 *v* 90% with MMR containing HPV-77:DE-5 rubella; significance assessment not reported).

Harms: The RCT assessed adverse effects in children with seroconversion, and found that fewer children receiving monovalent mumps than MMR immunisation had rash (2% with monovalent mumps *v* 17% with MMR containing rubella RA 27/3 *v* 20% with MMR containing rubella HPV-77:DE-5 immunisations) or fever (22% with monovalent mumps *v* 36% with MMR containing rubella RA 27/3 *v* 30% with MMR containing rubella HPV-77:DE-5 immunisations). [114] However, it found that more children having monovalent mumps immunisation had local reactions (14% with monovalent mumps *v* 8% with MMR containing rubella RA 27/3 *v* 5% with MMR containing rubella HPV-77:DE-5 immunisations; significance not reported for either outcome). It found similar rates of respiratory symptoms, lymphadenopathy, and sore eyes. The RCT is likely to have been underpowered to detect other clinically important adverse effects.

Comment: The RCT compared monovalent measles, mumps, and rubella immunisations versus MMR immunisation and is reported separately in all relevant options. [114] See also comment on Monovalent measles immunisation or combined MMR immunisation versus placebo or no immunisation, p 4
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QUESTION What are the effects of rubella immunisation?

OPTION MONOVALENT RUBELLA IMMUNISATION OR COMBINED MMR IMMUNISATION

Treatment effectiveness (clinical cases; rates of seroconversion)
Compared with placebo or no immunisation Two RCTs, population-based surveillance studies, and other observational studies in a range of different countries, found consistent evidence that rubella immunisation (MMR or monovalent) reduced the incidence of rubella infection.

Adverse effects
Compared with placebo or no immunisation One RCT, cohort studies, and population-based studies have found that MMR immunisation was associated with increased rates of fever and febrile seizures, although febrile seizures were rare, and there was no evidence of increased rates of afebrile seizures. Observational studies found that MMR containing some immunisation virus strains was associated with an increased risk of aseptic meningitis, and MMR immunisation was also associated with an increased risk of idiopathic thrombocytopenic purpura and arthralgia. Observational studies found no evidence of an association between MMR immunisation and the risks of developing asthma, type 1 diabetes, Guillain–Barré syndrome, gait disturbance, multiple sclerosis, optic neuritis, autism or autistic spectrum disorders, leukaemia, or inflammatory bowel disease. Anaphylaxis has been reported after immunisation with MMR, but this is rare.

Note:
RCTs using a control group receiving no immunisation or placebo are now deemed unethical, because of the existing evidence of efficacy of the MMR immunisation, and because of the potential harms associated with naturally acquired measles, mumps, or rubella infection. Rubella infection is usually mild, but can lead to fetal death or severe congenital abnormalities if contracted in early pregnancy.

Benefits:

RCTs of rubella in people receiving MMR or monovalent rubella immunisation versus placebo:
We found no systematic review, but found one RCT conducted in Taiwan in 1968, [129] and one RCT conducted in Japan in 1969. [130] The first RCT followed 11,670 primary-school children for about 1 year during a rubella outbreak in Kaohsiung, Taiwan. [129] The RCT compared six interventions: MMR containing HPV-77-GMK rubella strain (measles and mumps strains not reported; 186 children); monovalent rubella immunisations (HPV-77-GMK [183 children]; HPV-77 DECC [187 children]; and RA 27/3 [198 children]); placebo (using either monovalent measles or mumps immunisation [276 children]); and no immunisation (4420 boys; 5578 girls). [129] Only male children were immunised. The RCT found that fewer children receiving immunisation (MMR or any strain of monovalent rubella) developed rubella compared with children receiving placebo or no immunisation (0.5% with MMR, rubella HPV-77 DECC, and rubella RA 27/3; 0% with rubella HPV-77-GMK; 13% with measles placebo; 17% with mumps placebo; 13% of males with no immunisation; 16% of females with no immunisation).

The second RCT conducted during an outbreak in Japan (385 male students aged 16–18 years) compared RA 27/3 rubella immunisation (86 students) versus no immunisation (299 students). [130] During the first 2 weeks after immunisation, the rates of clinical rubella were similar in both groups. However, of those 85 people who were seronegative at the time of immunisation, significantly fewer immunised students developed rubella more than 14 days after immunisation compared with non-immunised students (0/24 [0%] with immunisation *v* 41/61 [67%] with no immunisation; P <0.001).

Population-based surveillance studies of rubella and congenital rubella syndrome incidence after MMR or monovalent rubella immunisation:
We found seven studies undertaken in the USA, Australia, and Europe. [131] [132] [133] [134] [135] [136] [137] [138] Passive population surveillance found that, with the decrease in the incidence of rubella in the USA after an effective childhood MMR immunisation programme, the number of infants born with congenital rubella syndrome (CRS) declined from 20 to 70 annual cases in the 1970s to only two annual cases by 1985. [131] In the late 1960s, only school-aged American children were immunised, and this had less effect in people older than 15 years, 10% to 20% of whom remained susceptible to rubella infection. This susceptibility was similar to preimmunisation years, and CRS continued to occur at an endemic level of an annual average of 32 cases between 1971 and 1977. With increased efforts to immunise high-school students and younger adults in the late 1970s in the USA, together with the introduction of MMR for routine use in young children, there was a rapid decrease in incidence of rubella in postpubertal age groups, resulting in a dramatic decrease in CRS. Figures obtained between 1996 and 2004 show a declining trend in the annual number of rubella cases recorded in the USA (23 in 2001; 18 in 2002; 7 in 2003; and 9 in 2004), and that 50% of these cases occurred in people born outside the USA. [132] Moreover, between 2001 and 2004, the time between reported cases increased, and each state and major city in the USA had at least 1 year during which no cases of rubella were identified. [137] Five cases of CRS were reported between 2001 and 2004: three born in 2001; one in 2003; and one in 2004. Four in five mothers with CRS babies were born in countries outside of the USA. The epidemiological evidence strongly suggests that endemic transmission of rubella has been absent in the USA since 2001. [137] One retrospective study of hospital records in Australia in 2000 (65,227 people) found that significantly more women born overseas were seronegative for rubella, and therefore at risk of having children with CRS. [133] In Sweden, a universal two-dose MMR immunisation regimen was introduced in 1982, and over 90% coverage was achieved. [134] Before this, in 1973, immunisation of 12-year-old girls against rubella had been introduced. Population surveillance found that the proportion of seronegative pregnant women reduced from 12% in 1975 to just below 2% in 1994. Before 1974, 14 cases of CRS were reported annually; since 1985, no cases have been reported. [134] However, population surveillance suggests that the incidence of rubella in the European region remains high, with a large number of cases reported from the Russian Federation (125,187 cases) and Romania (120,377) in 2003. [135] Between 2001 and 2003, 47 cases of CRS were reported, one third of which were from Romania, which experienced a large rubella outbreak in 2003 with over 115,000 reported cases. Romania did not have universal MMR immunisation at this time, although immunisation campaigns targeting school-aged girls began in 1998. [136] Rubella outbreaks also occur in non-immunised pockets. In 2004, in a Dutch religious community, there were 387 serologically confirmed cases of rubella, 29 of which were pregnant women. [138] By 2005, eight of the 16 children born out of these pregnancies had evidence of active infection. Three babies were born with multiple congenital deformities, and one baby had isolated auditory defects. In early 2005, it was noted that the outbreak had spread to Canada, to a community with religious and social links to the aforementioned Dutch religious community. [138]

Outbreak analyses of rubella and CRS incidence after MMR or monovalent immunisation:
We found two analyses. [139] [140] In Greece, immunisation of children aged 1 year with MMR was introduced in the mid-1970s, without any policies to attain high immunisation coverage or specifi-

cally to protect adolescents and young women. [139] Immunisation coverage in the late 1970s and 1980s remained consistently below 50%, and did not reach 50% to 60% before 1990. A major rubella epidemic in 1993 affected women of childbearing age at a higher rate compared with previous epidemics, showing a shift in the age of those infected. In the following year, 25 babies with CRS were admitted to hospital (24.6 cases/100,000 live births); seven of whom died. [139]

An outbreak of rubella in Brazil between 1999 and 2000 predominantly affected adolescents and young adults (age group 12–19 years compared with age group 1–4 years: RR of disease 3.7, 95% CI 2.4 to 5.8), resulting in 391 serologically confirmed rubella cases. Active surveillance was carried out for CRS in infants of women with confirmed rubella, and five infants with CRS were identified. In four cases, the mother had been infected in the first trimester of pregnancy. [140] Although Brazil had used routine childhood rubella immunisation in 1992, it was introduced in a phased manner (state by state). Rubella immunisation targeting children aged 1 to 11 years old was introduced in April 2000 in the state where the outbreak occurred, in the same month in which the epidemic began.

Harms: For harms of MMR immunisation see monovalent measles immunisation or combined MMR immunisation versus placebo or no immunisation, p 4 .

Comment: See comment on monovalent measles immunisation or combined MMR immunisation versus placebo or no immunisation, p 4 .

OPTION — MMR VERSUS MONOVALENT RUBELLA IMMUNISATION

Treatment effectiveness (clinical cases; rates of seroconversion)
MMR compared with monovalent rubella immunisation We found insufficient evidence from one RCT on whether MMR and monovalent rubella immunisation differ in effectiveness in increasing seroconversion rates. We found no evidence comparing the clinical effects of MMR and monovalent rubella immunisation.

Benefits: We found no systematic review or RCTs comparing the clinical effects of MMR versus monovalent rubella immunisation. We found one RCT (502 children aged 15 months to 4 years) comparing seroconversion rates of monovalent measles (Moraten strain), monovalent mumps (Jeryl-Lynn strain), or monovalent rubella (both RA 27/3 and HPV-77:DE-5 strains) versus seroconversion rates of their trivalent MMR counterpart (MMR containing Moraten measles plus Jeryl-Lynn mumps plus RA 27/3 rubella or MMR containing Moraten measles plus Jeryl-Lynn mumps plus HPV-77:DE5 rubella). [114] The RCT found similar rubella seroconversion rates with monovalent rubella immunisations and both MMR immunisations (100% with monovalent rubella RA 27/3 *v* 95% with monovalent rubella HPV-77:DE-5 *v* 100% with MMR containing rubella RA 27/3 *v* 99% with MMR containing rubella HPV-77:DE-5; significance assessment not reported).

Harms: The RCT assessed adverse effects in children with seroconversion, and found that fewer children receiving monovalent rubella than MMR immunisation had arthritis or arthralgia (0% with monovalent rubella *v* 0.7% with either MMR immunisation; significance not reported). [114] The RCT reported that the early onset of arthralgia in the two children receiving MMR suggests it was unrelated to immunisation. [114] The RCT also found that fewer children having monovalent rubella immunisation than MMR had fever (28% with monovalent rubella RA 27/3 *v* 19% with monovalent rubella HPV-77:DE-5 *v* 36% with MMR containing rubella RA 27/3 *v* 30% with MMR containing rubella HPV-77:DE-5 immunisations) and rash (11–13% with monovalent immunisation *v* 17–20% with MMR; significance not reported). More children receiving MMR containing RA 27/3 rubella had lymphadenopathy (8% with MMR containing RA 27/3 *v* 4% with other rubella immunisations). There were similar rates of local reactions, respiratory symptoms, and sore eyes between monovalent rubella immunisation and MMR immunisation. The RCT is likely to have been underpowered to detect other clinically important adverse effects.

Comment: The RCT compared monovalent measles, mumps, and rubella immunisations versus MMR immunisation and is reported separately in all relevant options. [114] See also comment on monovalent measles immunisation or combined MMR immunisation versus placebo or no immunisation, p 4
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GLOSSARY

Developmental regression is defined as loss of acquired developmental skills.
Seroconversion Development in the blood of specific antibody to the infective agent. Seroconversion is a proxy for clinical efficacy.
Yellow cards A passive reporting system, in which a health professional becomes aware of a significant adverse event after a medication has been given and reports this to the UK Committee on Safety of Medicines using a specific yellow card.

Autistic spectrum disorders are defined by early onset (diagnosed at <36 months) of difficulties in social reciprocity and communication as well as restrictive, repetitive behaviour. The disorders include autistic disorder, childhood disintegrative disorder, Rett's syndrome, and Asperger's disorder.
Case crossover study is in effect the same as a self-controlled case series, in which each person serves as his or her own control.
Combined measles, mumps, and rubella (MMR) immunisation Immunisation with components that aim to raise immunity to measles, mumps, and rubella infections. Contains live attenuated measles virus (Schwarz strain).
DTP Diphtheria, tetanus, and pertussis combined immunisation.
Health maintenance organisation (HMO) These are medical centres in the USA that have primary, secondary, and tertiary medical-care facilities and are generally funded by private healthcare insurance. The relevance of HMOs is their participation in the Vaccine Safety Datalink (VSD) project set up by the Centers for Disease Control and Prevention (CDC) in 1991. This project links medical event information, immunisation history, and selected demographic information from the computerised databases of four staff HMOs: Group Health Co-operative of Puget Sound in Seattle, Kaiser Permanente Northwest in Portland, Kaiser Permanente Medical Care Program of North California in Oakland, and Southern California Kaiser Permanente in Los Angeles.
Herd immunity Background level of immunity in the community. A high level of herd immunity reduces the risk of infection even in non-immune individuals, because there is no pool of at-risk individuals who may transmit the infectious agent.
Immunisation coverage Prevalence of immunisation in the community.
Immunisation efficacy An estimate of the proportional reduction in cases associated with the use of an immunisation. Efficacy % = (1 – [attack rate in immunised/attack rate in non-immunised] x 100).
Self-controlled case series A case series in which people act as their own controls by comparing event rates within a defined time period of exposure with earlier, later, or both periods. [67]

SUBSTANTIVE CHANGES

Monovalent measles immunisation or combined MMR immunisation versus placebo or no immunisation: Three self-controlled case series added to harms, which found increased rates of febrile convulsions, idiopathic thrombocytopenic purpura (ITP), fever, rash, and diarrhoea after MMR immunisation. One self-controlled case series added to harms, which found no cases of aseptic meningitis after MMR immunisation containing RIT 4385 mumps immunisation strain. Categorised as Beneficial.
Monovalent rubella immunisation or combined MMR immunisation versus placebo or no immunisation: One population-based study added to benefits, which found that endemic cases of rubella were rare in the USA between 2001 and 2004. One case study added to benefits, reporting an outbreak of rubella in a non-immunised community. Categorised as Beneficial.

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Competing interests: HB, DE, and NS have in the past received money from immunisation manufacturers to attend symposia and conduct research. HEB declares that they have no competing interests

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TABLE 1 **Strain combinations of MMR immunisations.**

Measles component	Mumps component	Rubella component
Enders–Edmonston B	Jeryl-Lynn	RA 27/3
Schwarz	Urabe Am 9	RA 27/3
Edmonston–Zagreb	Rubini	RA 27/3
Edmonston–Zagreb	Jeryl-Lynn	RA 27/3
Schwarz	RIT 4385	RA 27/3
Schwarz	Jeryl-Lynn	Cendehil
Edmonston–Zagreb	Jeryl-Lynn	HPV-DE 55